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REVIEW

Evidence-based prescribing of medications for ADHD: where are we in 2023?

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ABSTRACT

Introduction: A large number of randomized controlled trials (RCTs) and observational studies on the pharmacotherapy of ADHD are available.

Areas covered: Based on a search in PubMed and PsycInfo (up to 15 September 2022), this review addresses to which extent this body of research is currently able to inform routine prescribing practice, in terms of the choice of medication, titration strategy, augmentation treatments, and use of alternative, non-approved treatments.

Expert opinion: A growing body of evidence is informing prescribers on some, but certainly not all, aspects related to the pharmacological treatment of ADHD in the daily clinical practice, with important weaknesses/ gaps that need to be addressed. First, evidence synthesis of RCTs is not able to inform decision-making at the individual patient level. Second, the maximum safe and effective doses, possibly beyond those currently recommended, are not well understood. Third, evidence from RCTs on augmenting strategies is still limited. Fourth, no novel agents with the same or higher effect size of stimulants, in terms of efficacy, but with better tolerability and lower abuse potential, have been found. Implementation of precision psychiatry approaches and stratification of patients in future RCTs will be key to, respectively, individualize the treatment strategies and test etiopathophysiology-based agents.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is defined by impairing, developmentally inappropriate, and pervasive symptoms of inattention and/or hyperactivity [1]. Symptoms associated with functional impairment persist in adulthood in a substantial portion of individuals with childhood onset symptoms, even if they do not meet the formal criteria for the disorder as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 [1] or in the International Classification of Diseases (ICD)-11 [2].

If not effectively treated, ADHD can lead to negative outcomes, including increased risk of substance abuse, antisocial behaviors, and increased risk of accidents and mortality [3].

Pharmacological treatment, including stimulant and non-stimulant options, is an important component of the multimodal treatment strategy for individuals with ADHD [4]. Currently, Food and Drug Administration (FDA)-approved stimulants for ADHD include methylphenidate and amphetamine preparations. FDA-approved non-stimulant medications encompass atomoxetine, clonidine and guanfacine extended-release, and viloxazine [4].

Since the study published by Bradley [5] in 1937 reporting the beneficial effects of an amphetamine compound (benzedrine) on ADHD symptoms in children, and the approval of methylphenidate by the FDA in 1955, a large number of randomized controlled trials, observational investigations, and meta-

analyses of such studies have been published. Indeed, ADHD and its pharmacological treatment are among the most investigated topics in child and adolescent psychiatry [6]. This body of evidence informs our knowledge on the clinical pharmacology of ADHD. This review summarizes the currently available key evidence that can potentially inform each step related to the prescription of ADHD medications in clinical practice, from the initial selection of the most appropriate agent to the follow-up of a stabilized regimen, highlighting the gaps and needs in terms of evidence base. This will be preceded by an introductory section on the evidence related to prescription rates of ADHD medications in the past decades, which should be essential knowledge for any prescriber in the field.

Articles included in this review were retrieved via a search in PubMed and PsycInfo (up to 15 September 2022) of relevant papers (mainly meta-analyses, supplemented by individual trials) using search terms for ADHD and pharmacotherapy.

2. Evidence on the prevalence of ADHD medication use across the world

In 2018, Raman et al. [7] published a large-scale study including data on ADHD medication use prevalence from 13 countries (four in Asia and Australia, two in North America, five in Northern Europe, three in Western Europe, and one Special

Article highlights

- A large body of evidence from randomized controlled trials show that medications for ADHD, in particular stimulants, are highly efficacious, at least in the short term, for ADHD core symptoms
- Self-controlled studies also show that stimulant use is associated with a significant reduction of negative outcomes such as unintentional physical injuries, motor vehicle accidents, criminal acts, substance use disorder, seizures, and depression.
- Currently, prescribers still use a trial and error process to find the best medication for each patient with ADHD
- A precision psychiatry approach is needed to tailor the choice of the medication to the specific characteristics of the patient
- Additional evidence is needed to inform strategies for the management of individuals who do not respond to stimulants
- Longer-term effects of medications for ADHD require further investigation

Administrative Region in China) encompassing a total of 154.5 million individuals (>3 years old) in the period 2001–2015. In 2010, in children, ADHD medication use prevalence varied from 0.27% (France) to 6.69% (USA, according to Medicaid database) across the included countries (0.95% in Asia and Australia, 4.48% in North America, 1.95% in Northern Europe, and 0.70% in Western Europe). From 2011 to 2015, medication use prevalence increased in all included countries, with average yearly relative percentage increases spanning from 2.83% (in the USA) to 45.11% (in Canada). Across the world, methylphenidate was the most commonly used medication for ADHD. In adults, the prevalence of ADHD medication use was lower compared to that in children, varying between 0.003% and 1.48%. Like in children, in adults there was an increase in the prevalence of medication use from 2001 to 2015, with average yearly relative percentage increases ranging from 7.94% (in Taiwan) to 75.88% (in Japan). The increase in medication use might be of concern, and indeed it is usually pictured in such a way by the lay press. However, the key question for clinicians, commissioners of clinical services, policy makers, and guidelines group members should be: 'Are all children with ADHD who would benefit from a pharmacological treatment indeed being treated with medications for ADHD?' rather than 'Has the prevalence of ADHD medication use increased over time?' The data presented by Raman et al. [7] show that in some countries, from 2001 to 2015, the prevalence of the use of ADHD medications has increased from very little to little, both in children (e.g. UK, from 0.30% to 0.64% or Hong Kong, from 0.003% to 0.01%) and in adults (e.g. Spain, from 0.02% to 0.1%). However, other figures, in particular those for the USA, are more substantial. Nonetheless, they are still on average lower than the expected, estimated prevalence of ADHD (around 5–7% [8] in children and 4% [9] in adults). So overall, these data suggest that many individuals who could benefit from ADHD medications are not treated. It is also possible that some of the individuals who receive treatment do not have ADHD. A systematic review with meta-analysis [10,11] addressed this issue by including 36 observational studies (encompassing a total of 104,305 individuals) and meta-analyzing data from 18 studies reporting the rate of ADHD pharmacological treatment in both diagnosed and undiagnosed individuals. Results showed that 19.1% and 0.9% of school-age children/adolescents with and without

ADHD, respectively, were treated with ADHD medications. Moreover, the authors of this meta-analysis estimated that, based on previous sequential treatment studies (e.g. [12]), at least 70% of the children and adolescents with a proper ADHD diagnosis might benefit from a trial with ADHD medication after behavioral therapy has been tried. Based on this assumption, the authors concluded that, in the USA, for each person using medication without a formal ADHD diagnosis, there would be three patients with a formal diagnosis who might benefit from medication but did not receive it. Alongside other stakeholders, clinicians should be aware of these data to reflect about their practices.

This review examines now in detail the different steps involved in the prescription of ADHD medications, highlighting to which extent they are informed by empirical evidence.

3. Psychoeducation on the effects of ADHD medications in 'real world'

Before starting a pharmacological treatment for ADHD, psychoeducation, including the effects of the pharmacological treatment, is key. When discussing the pros and cons of starting a pharmacological treatment for ADHD, prescribers should strive to provide the most updated and the highest-level quality available. In addition to information from RCTs (see next section), it is valuable to discuss, using a language adapted to the level of understanding of the patients and their families, also data from observational studies, which focus on outcomes that are typically not included in RCTs (either because rare – albeit important – or because it would be logistically challenging or too expensive to include such outcomes). However, the main issue with observational studies is represented by confounding by indication. In other terms, if a significant difference emerges between individuals treated and those not treated on a specific outcome, the absence of randomization will not allow one to understand if the difference is due to the medication effects per se or to baseline differences in the characteristics of the individuals exposed and of those not exposed to the treatment. A particular observational design referred to as *self-controlled* (or *within individual*) allows one to partially address this issue. In this design, the outcome is measured when the individual is on and off medication (there is still some bias related to the different timing of the measurement, but this can be statistically controlled, at least in part). As reviewed by Chang et al. [13], large-scale self-controlled studies have shown that, compared to periods when they were off ADHD medications, in periods when they were on ADHD medications, individuals with ADHD presented with significantly reduced rates of unintentional physical injuries, motor vehicle accidents (in males), criminal acts, substance use disorder, seizures, and depression. Additionally, they did not show significantly different rates of suicidality or psychosis. Those with bipolar disorder had an exacerbation of manic symptoms if they were not receiving concurrent treatment with mood stabilizers, but presented with decreased severity of manic symptoms when they were treated with stimulants alongside mood stabilizers. Regarding

the risk of suicidality, another study [14] showed that it was higher than expected before starting methylphenidate in youth ages 6–25, it declined (but was still higher than expected) during the 90 days following the treatment, and then it further declined to levels comparable to those found in non-treated individuals. Overall, this study does not support a causal effect of methylphenidate in terms of increasing the risk of suicidal ideation. It is possible that higher levels of suicidality before treatment reflect a stressful period in a life of an individual with ADHD, which triggered a referral to a psychiatrist with a subsequent a decision to begin ADHD treatment; once the regimen of methylphenidate is stabilized, the risk of suicidal behaviors would decrease to non-significant. It is also of course possible that this decreased risk could be accounted for by the human interaction with a clinician.

4. Initial choice of the medication

Once a decision of starting a pharmacological intervention has been made and appropriate psychoeducation on ADHD and its treatment has been delivered, prescribers, jointly with their patients and their parents/carers, need to choose among an array of possible options, which are more or less broad depending on the availability and licensing of specific medications and formulations in each country. Ideally, evidence to support this shared decision-making process would come from head-to-head RCTs comparing two or more active medications in terms of efficacy, tolerability, or other specific clinically relevant outcomes (e.g., blood pressure). However, in the field of ADHD (and other disorders in child and adolescent psychiatry) such head-to-head trials are quite rare, with the majority of available RCTs comparing active medication to placebo. In this respect, network meta-analyses (NMA) can provide useful information. This particular type of meta-analysis, under certain methodological assumptions, allows one to compare two or more interventions in terms of efficacy, tolerability, or other outcomes, even when these interventions have not been compared head-to-head in the individual RCTs included in the NMA [15]. Under certain assumptions, evidence from NMA is considered more precise than the one from standard (i.e. pairwise) meta-analyses, as they combine direct and indirect evidence [16]. Therefore, this section covers key NMAs in the field, rather than pairwise meta-analyses.

On behalf of the European ADHD Guidelines Group (EAGG), Cortese et al. [17] conducted a systematic review and NMA of 133 RCTs (81 in children and adolescents, 51 in adults, and one in both), including a total of 14,346 children and adolescents and 10,296 adults. The authors searched publicly available databases and gathered published data from drug companies and study authors. While the authors initially set out to assess the medication effects in the short (RCTs duration closest to 12 weeks), medium (closest to 26 weeks) and longer terms (closest to 52 weeks), the vast majority of RCTs selected for inclusion assessed outcomes closest to 12 weeks. The NMA aimed to compare ADHD medications against placebo and among them on the following outcomes: efficacy (i.e., reduction of ADHD symptoms severity – co-primary outcome), tolerability (i.e., number of individuals who drop out from the RCT due to adverse events

– co primary outcome), clinical global impression-improvement (CGI-I) score, acceptability (i.e., number of individuals who drop-out from the RCT due to any cause), blood pressure, and weight. Cortese and colleagues included both licensed (i.e., amphetamines, methylphenidate, atomoxetine, clonidine (XR), and clonidine (XR)) and not licensed medications for ADHD but for which RCTs were available (i.e., modafinil and bupropion) (of note, when the protocol of the NMA [18] was designed, viloxazine was not FDA-approved yet).

In relation to efficacy, results showed that, based on ratings by clinicians in children and adolescents, all drugs were better than placebo. In adults, stimulants (amphetamines, methylphenidate), bupropion, and atomoxetine were better than placebo. However, modafinil was not better placebo. Given the paucity of data for clonidine and guanfacine, no analyses could be conducted for these two compounds. In relation to drug-to-drug comparisons, amphetamines were significantly superior to modafinil, atomoxetine, and methylphenidate in children-adolescents and in adults. Moreover, in children and adolescents, amphetamines were better than guanfacine, and methylphenidate was better than atomoxetine. In adults, methylphenidate, atomoxetine, and bupropion were better than modafinil. However, based on teachers' ratings of the severity of ADHD symptoms, only methylphenidate and modafinil were better than placebo (given the lack of data on teachers' ratings in RCTs of amphetamines and clonidine, no analyses could be conducted for these two compounds). Results based on parents' rating were substantially replicated when considering efficacy based on parents' ratings of ADHD symptoms severity and adults' self-ratings of the severity of own ADHD symptoms, with the exception of guanfacine, which was not different from placebo based on parents' ratings, and bupropion, which was not better than placebo based on parents' ratings and adults' self-report. Considering the other co-primary outcome, i.e. tolerability, in RCTs of children and adolescents, guanfacine and amphetamines were worse than placebo, while the other medications were not significantly different from placebo. In adults, modafinil, amphetamines, methylphenidate, and atomoxetine were worse than placebo (no data were available from RCTs of guanfacine and clonidine). No significant differences in tolerability were found across active drugs, in children, adolescents, and adults. Post-hoc analyses in which lisdexamfetamine was analyzed separately from other amphetamines showed that, in children, it was less well tolerated compared with placebo, whereas tolerability of the other amphetamines was slightly better. In adults, the opposite pattern was found, but this was a *post hoc* analysis should be interpreted with caution given the limited number of RCTs. Regarding the secondary efficacy outcomes (CGI-I scores) in children/adolescents, all agents were superior to placebo, with the exception of clonidine. In adults, amphetamines, bupropion, and methylphenidate were superior to placebo. In terms of other secondary outcomes, in children and adolescents, it was found that systolic blood pressure was increased with amphetamines and atomoxetine, compared with placebo. In adults, this was the case for methylphenidate. Amphetamines, atomoxetine, and methylphenidate in children and adults, and atomoxetine and methylphenidate in adults, were associated with

significantly increased diastolic blood pressure compared with placebo. Finally, in children and adolescents, weight was significantly decreased, compared with placebo, in individuals treated with amphetamines, methylphenidate, atomoxetine, and modafinil. In adults, this was the case for amphetamines and methylphenidate. A summary of the findings of the NMA is provided in Table 1.

Cortese et al. concluded that, considering both efficacy and tolerability in children, evidence would support methylphenidate as the first-line choice, because, even if it is less efficacious than amphetamines, it is better tolerated (compared to placebo). By contrast, in adults, amphetamines would rank as the preferred treatment. This is quite consistent with the 2019 National Institute for Health and Care Excellence (NICE) guidelines on ADHD [19] that recommend methylphenidate as first-line treatment in children (followed by amphetamines) and amphetamines or methylphenidate as first line in adults.

Another NMA [20], based on 190 RCTs (including a total of 26,114 participants) compared, in the same network, pharmacological and non-pharmacological interventions for ADHD in children and adolescents (in total, 52 different types of interventions). This NMA found that behavioral therapy (as standalone treatment or combined with stimulants),

stimulants, and non-stimulant were better than placebo. Behavioral therapy combined with stimulants was better than stimulants or non-stimulants. Stimulants were better than behavioral therapy, cognitive training, and non-stimulants. Behavioral therapy, stimulants and their combination were the most acceptable treatments. No significant issues of tolerability were reported for stimulants and non-stimulants. Methylphenidate, amphetamine, atomoxetine, guanfacine, and clonidine were significantly more efficacious than placebo. Methylphenidate and amphetamine were better, in terms of efficacy, than atomoxetine and guanfacine. Methylphenidate and clonidine had better acceptability than placebo and atomoxetine. Pharmacological treatments were associated with adverse effects (such as decreased appetite, weight loss, and insomnia), but not with serious adverse events. There was no evidence to support the use of cognitive training, neurofeedback, antidepressants, antipsychotics, dietary therapy, fatty acids, and other complementary and alternative medicine. A note of caution should be used in interpreting these findings, as combining pharmacological and non-pharmacologic interventions in the same network may be hampered by a number of methodological issues [21].

Table 1. Summary of the findings of the network meta-analysis by Cortese et al. [17].

Medication (in alphabetical order)	Effect size on ADHD core symptoms (total) vs placebo	Effects size on other aspects of functioning vs placebo
Dex-amphetamine (including lisdexamfetamine and mixed amphetamine salts)	Teachers' ratings- Clinician's ratings SMD = 1.02 (0.85 to 1.19) Parents' ratings SMD = 1.07 (0.79 to 1.36)	Clinical global functioning OR = 7.71 (5.52 to 10.77)
Atomoxetine	Teachers' ratings SMD = 0.32 (−0.18 to 0.82) Clinician's ratings SMD = 0.56 (0.45 to 0.66) Parents' ratings SMD = 0.60 (0.50 to 0.71)	Clinical global functioning OR = 2.28 (1.38 to 3.76)
Bupropion	Teachers' ratings SMD = 0.32 (−0.43 to 1.07) Clinician's ratings SMD = 0.96 (0.22 to 1.69) Parents' ratings SMD = −0.24 (−0.92 to 0.44)	-
Clonidine	Teachers' ratings- Clinician's ratings SMD = 0.71 (0.24 to 1.17) Parents' ratings not available	Clinical global functioning OR = 2.78 (0.91 to 8.53)
Guanfacine	Teachers' ratings SMD = 0.63 (−0.35 to 1.62) Clinician's ratings SMD = 0.67 (0.50 to 0.85) Parents' ratings SMD = 0.23 (- 0.45 to 0.90)	Clinical global functioning OR = 3.63 (2.36; 5.57)
Methylphenidate	Teachers' ratings SMD = 0.82 (0.48 to 1.16) Clinician's ratings SMD = 0.78 (0.62 to 0.93) Parents' ratings SMD = 0.84 (0.72 to 0.95)	Clinical global functioning OR = 5.57 (3.99 to 7.79)
Modafinil	Teachers' ratings SMD = 0.76 (0.37 to 1.15) Clinician's ratings SMD = 0.62 (0.41 to 0.84) Parents' ratings SMD = 0.46 (0.31 to 0.61)	Clinical global functioning OR = 3.22 (1.91 to 5.43)

SMD, standardized mean difference; OR, odds ratio.

5. The relevance of placebo effect

When providing information to the patients and their families on the medication that has been chosen, it may be relevant also to rely on the possible placebo effect that may contribute to the effects of the chosen medication. A meta-analysis of 128 double-blind RCTs (including a total of 10,578 children/adolescents and 9,175 adults), drawing on the dataset of the NMA by Cortese et al. [17], found significant placebo effects, i.e., some participants assigned to placebo did present with an improvement in terms of efficacy, in particular when this was rated by clinicians. There was a significant correlation between the baseline to endpoint placebo effects and the baseline to endpoint drug effects, except when considering self-ratings. Therefore, decreases in symptoms due to expectation of benefit and other factors related to the psychosocial context of treatment were found not only in participants on placebo, but also on those receiving active medication. These findings suggest that active drug effects in the included RCTs likely combine the improvement related to the placebo and that specifically attributable to the active medication. The authors suggest that the results of their meta-analysis may have important implications for the clinical practice. Indeed, in line with the guidelines of an international consensus group [22], clinicians prescribing ADHD medications could leverage the placebo effect by incorporating factors known to produce placebo effects in the delivery of care, such as creating a trusting, warm, and empathic patient–clinician relationship, and optimizing the patient's expectation of benefit. The international consensus group has also suggested the use of open-label placebo prescriptions, but this has not been tested/validated yet for ADHD.

6. Dose optimization

Once a pharmacological treatment is started, optimizing it, i.e., properly titrating the dose considering the benefit/risk trade-off and providing an appropriate coverage during the day based on the needs of the patients and their families, is key. Meta-analytic evidence supports this practice. In a dose–response meta-analysis of 65 RCTs (including 7,877 children/adolescents), drawing on the dataset by Cortese et al. [17], Farhat et al. [23] found that, when pooling data from fixed-dose trials of methylphenidate or amphetamines, there were increased efficacy and increased likelihood of discontinuation due to adverse events with increasing doses of stimulants. The incremental benefits of stimulants in terms of efficacy decreased when doses were titrated beyond 30 mg/day for methylphenidate or 20 mg/day of amphetamines. By contrast, meta-analyses of flexible-dose trials for both methylphenidate and amphetamines showed increased efficacy alongside reduced likelihood of discontinuations for any reason with increasing stimulant doses. These incremental benefits of psychostimulants in terms of efficacy persisted across all the range of FDA-licensed dose both for methylphenidate and amphetamines. Overall, these results suggest that flexible titration, until the stimulant is well tolerated, is associated with the best efficacy and acceptability.

Of note, the maximum recommended doses of psychostimulants for the treatment of ADHD in guidelines or formularies may be higher than the maximum doses licensed by regulatory agencies such the Food and Drug Administration (FDA) or the European Agency (EMA). For instance, the maximum licensed dose of methylphenidate for children (except for osmotic release and prolonged release formulations, see below) is 60 mg/day, while the British National formulary (BNF) [24] recommends a dose of up to 90 mg/day, under the direction of a specialist. For osmotic-release (e.g., Concerta ® XL) and other prolonged-release formulations of methylphenidate (e.g., Xaggitin ® XL and Delmosart ® prolonged-release tablet), the maximum license dose is 54 mg/day, but the BNF mentions a maximum of 108 mg/day for Concerta ® XL, in line with other clinical guidelines, e.g., those from the Canadian ADHD Resource Alliance (CADDRA) (caddra.ca). For lisdexamfetamine, both the maximum licensed *and* the BNF recommended dose is 70 mg/day. In clinical practice, many prescribers will use doses above the maximum licensed ones. Some of them will also use doses beyond the maximum recommended in guidelines/formularies. Currently, there is no solid, meta-analytic evidence to inform if, and to what extent, doses beyond the recommended ones are safe and bring additional efficacy/effectiveness. Some experts suggest that, while it should not be a standard, routine practice, using doses beyond the maximum recommended ones could be an option when the patient has presented with a partial response, there is only some degree of improvement at the maximum recommended dose, tolerability is good, and the aim is to optimize the response [25]. This could be considered particularly in individuals with overweight/obesity when a partial response was obtained at the licensed dose and tolerability has been satisfactory. However, if doses beyond those recommended are used, a careful monitoring of blood pressure, heart rate, height, and weight should be implemented.

7. Lack of response to psychostimulants

Following poor response to two stimulants (methylphenidate and amphetamines), some clinicians would quickly move to second- or third-line approved compounds, unlicensed medications for ADHD, or combinations of different agents. However, a number of factors should be assessed before switching to alternative medications or using polypharmacy. Indeed, it should be highlighted that the majority of patients with ADHD respond to one or both classes of psychostimulants, when used properly. A review [26] of RCTs found that around 40% of children treated with immediate-release stimulants responded equally well to amphetamine or methylphenidate, nearly 38% responded better to amphetamines, around 15% had a better response to methylphenidate, and around 15% did not respond to either medication. A more recent review showed that around 90% of the individuals with ADHD respond to either or both class of stimulants [27]. However, a note of caution should be expressed on these figures; as RCTs often exclude participants with specific comorbidities that may decrease the rate of response, the response rate in patients seen in daily clinical practice may be lower. Nonetheless, the fact that a large portion of individuals with

ADHD respond well to at least one of the two stimulants, suggests that, before moving to alternative agents and/or polypharmacy, a number of factors (summarized in Table 2) should be considered. These are summarized in the following questions: (a) *Has an appropriate titration occurred*? As mentioned, while some patients will respond well to low or moderate doses, others will need higher ones, regardless of their age and weight [23]; (b) *Is this medication providing the required coverage across the day or is a change in the formulation needed to get a more comprehensive coverage*? Indeed, parents may report poor response, but this may refer to the period of the day when the medication effect has worn off; (c) *Are the 'right' symptoms being targeted*? Psychostimulants are in general highly efficacious/effective on the core symptoms of ADHD (i.e., inattention, hyperactivity, impulsivity) [4], not necessarily on other problems (e.g. oppositional behavior/emotional dysregulation); (d) *Is the patient showing tolerance*? Evidence from clinical studies, e.g., [28], shows the need to increase the dose of stimulants over time in order to maintain therapeutic response. Additionally, neuroimaging studies [e.g., PET studies [29]] point to an increase in dopamine reuptake receptors in adults with ADHD treated for up to 12 months with stimulants. This evidence suggests that tolerance may happen during treatment with psychostimulants, even though more research is needed to gain a better understanding of the exact percentage of patients who develop tolerance, their clinical characteristics, and how to manage tolerance effectively. Some experts, e.g., [30], suggest decreasing the dose or temporarily (for a few weeks) stop the stimulant to overcome the tolerance issues; (e) *What else is going on in patient's life/family life*? A comprehensive formulation, beyond diagnosis, is key here; (f) *Has any relevant comorbidity been missed*? Some comorbidities, e.g., autism spectrum disorder ([31]), are associated with lower chances of response; (g) *Is the diagnosis correct*?

Only after all these aspects have been assessed, the prescriber should consider (1) second-line medications (atomoxetine – which selectively inhibits the norepinephrine transporter, and guanfacine – that selectively stimulates alpha-2 adrenergic receptors, or clonidine, that selectively stimulates alpha-2A adrenergic receptors); (2) augmenting agents (guanfacine or clonidine XR); (3) other agents, under specialistic advice/supervision, for which RCTs provide preliminary evidence of efficacy (e.g., bupropion, a noncompetitive antagonist of nicotinic acetylcholine receptors) [25]. The

Table 2. Questions to consider when a patient with ADHD does not respond to stimulants.

(a) *Has an appropriate titration occurred*?
(b) *Is this medication providing the required coverage across the day or is a change in the formulation needed to get a more comprehensive coverage*?
(c) *Are the 'right' symptoms being targeted*?
(d) *Is the patient showing tolerance*?
(e) *What else is going on in patient's life/family life*?
(f) *Has any relevant comorbidity been missed*?
(g) *Is the diagnosis correct*?

evidence on combination of medications for ADHD is overall still limited. Cortese et al. [25] systematically reviewed studies on combined treatments. They did not find any RCT comparing stimulants plus placebo vs. stimulants plus atomoxetine. However, they found one small RCT ($n = 25$) [32] in which patients non-responders to atomoxetine were randomly assigned to either methylphenidate or atomoxetine augmentation. After 1 week, scores of ADHD symptoms severity were significantly better in groups assigned to atomoxetine plus stimulants, compared to the group on atomoxetine plus placebo, with no significant differences between the two groups being reported at week 10. Also, no significant differences within arms or between groups in relation to changes in blood pressure or pulse rate were reported. Regarding guanfacine XR, according to one large RCT ($n = 461$) [33] in children/adolescents guanfacine XR combined to stimulants was better than stimulants alone in reducing the ADHD symptoms severity. In another smaller RCT [34] in children/adolescents, d-methylphenidate ER combined to guanfacine immediate-release was superior to guanfacine alone, but not significantly different from d-methylphenidate ER, in decreasing ADHD core symptoms severity and improving working memory. Cortese et al. [25] also found two RCTS on clonidine as augmenting agent, the first [35] showing benefits in combining clonidine XR with stimulants in terms of reducing of ADHD core symptoms severity in children/adolescents, and the second [36] failing to confirm benefits on ADHD core symptoms, but showing significant effects on conduct symptoms.

8. Effects of non-core ADHD symptoms

Quite rarely individuals with ADHD treated in clinical services present only with ADHD symptoms. This section focuses in particular on two aspects that may be associated with ADHD: executive dysfunction and emotional dysregulation. Prescribers may wonder if the effects of ADHD medications on these aspects are similar to those found on core symptoms. The simple answer, based on currently available evidence, is no. In a meta-analysis of 60 RCTs, Coghill et al. [37] found that methylphenidate was superior to placebo in all five domains of executive dysfunction analyzed in the review, but effect sizes were lower than those found for ADHD core symptom (executive memory, standardized mean difference (SMD): −0.26, 95% confidence interval (CI): −0.39 to −0.13; non-executive memory, SMD=-0 .60, 95% CI: −0.79 to −0.41; reaction time, SMD= −0 .24, 95% CI: −0.33 to −0.15; reaction time variability, SMD = −0.62, 95% CI: −0.90 to −0.34; response inhibition, SMD = −0.41, 95% CI: −0.55 to −0.27.

Another meta-analysis [38] of 21 RCTs of studies in adults with ADHD found small-to-moderate effects size when considering effects on emotional dysregulation (methylphenidate: SMD = 0.34, 95% CI = 0.23–0.45; atomoxetine: SMD = 0.24, 95% CI = 0.15–0.34; lisdexamfetamine: SMD = 0.50, 95% CI = 0.21–0.8). However, it is important to stress the relevance of a proper optimization. In a RCT [39] comparing adjunctive risperidone, valproex sodium, or placebo for aggressive behaviors in children with ADHD and associated oppositional defiant disorder (ODD) or conduct disorder (CD), individuals with

aggressive symptoms persisting after an open-label optimization of psychostimulants entered the 8-week randomized phase, with weekly sessions of family-based during both the optimization and the randomized phases. Among the 151 participants who completed the optimization phase, unexpectedly, around 64% met the criteria for remission. Therefore, this RCT suggests that optimizing the dose of stimulants can reduce the need to use antipsychotic or mood stabilizers for emotional dysregulation associated with ADHD.

9. Longer-term effects

An important question that patients and families ask is: *Do the effects of the medication persist over time*? This is relevant as ADHD is often a chronic condition and, as such, it needs to be treated not only during a few weeks. Ideally, to provide evidence of long-term effects, one would need data from long-term RCT, but it is not ethical to randomize individuals to placebo when the active medications is highly efficacious in the short terms, as ADHD medications in particular stimulants, are. However, a particular study design, i.e., *discontinuation trial*, can provide information on longer-term effects. In one example [40] of such study design, a double-blind RCT of medication discontinuation, children/adolescents who had been treated with methylphenidate for an average of 4.5 years were randomly assigned to continue methylphenidate or discontinuing it (and being switched to placebo). The study found that continuation was associated with an ongoing benefit with respect to ADHD symptoms, compared with discontinuation and a switch to placebo. However, effect sizes for these benefits were smaller than those reported in short-term RCTs of methylphenidate in the short term. It is possible that this was due to decreased effectiveness of the medication over time, or the fact that adjustment of the dose was inadequate. It is also possible that this was linked to the fact that the trial recruited only mild cases, as many parents did not wish their child to take part in the study as they knew that if their child were assigned to placebo, a deterioration in behavior would occur. Therefore, longer-term effects of ADHD medications deserve additional investigation.

10. Non-medical use of ADHD medication

It is important for the prescriber to be aware of the evidence on non-medical use of ADHD medications. A systematic review [41] found that up to 58.7% of college students in the USA reported nonmedical use of stimulants on at least one occasion, and 2.1% of adults in the USA reported at least one episode of nonmedical stimulant use in the previous year. Reasons for this non-medical use included enhancement of academic or work performance and recreational use ('getting high'). Another possible explanation is self-medication for undiagnosed ADHD. Indeed, compared to those who did not, persons who did engage in nonmedical use of stimulants reported more symptoms of ADHD, but overreporting of ADHD symptoms in the studies included in the review is also possible. Of note, nonmedical stimulant use was associated with life-threatening symptoms in up to 0.4% of the users.

11. Medications in the pipeline

Prescribers may wonder which novel medications to consider, in the future, in cases who do not respond to licensed medications or other medications used for ADHD. Given that stimulants have a large effect size, it is unlikely that medications with even better effect size will be found. In a systematic review of 28 RCTs in clinicaltrials.gov, Nageye and Cortese [41] identified a number of agents currently being tested, including compounds acting on a plethora of biological targets, including vortioxetine, fasoracetam (NFC-1, AEVI-001), dasotraline, centanafadine SR (CTN SR), OPC-64005, metadoxine (MDX), tipepidine hibenzate, oxytocin, sativex (delta-9-tetrahydrocannabinol (THC) plus cannabidiol), mazindol, and molindone hydrochloride (SPN-810). Given the high effect size found in RCTs of stimulants in relation to their efficacy on ADHD core symptoms, these novel agents will unlikely show better efficacy than stimulants, at the group level. However, they may be comparable or better in terms of tolerability.

12. Conclusion

Currently, empirical evidence informs mainly the choice of medication at the group level and the effects of medications on short-term outcomes. Additional evidence is needed to tailor the treatment to specific characterizes of the patients and understand the effects of medications in the longer term.

13. Expert opinion

13.1. Key findings and weaknesses

Overall, there is a growing body of evidence to support prescribers in some, but certainly not all, the aspects related to the pharmacological treatment of ADHD in the daily clinical practice, with important weaknesses/gaps that need to be addressed. First, while there is a large body of evidence from RCTs to inform the selection of first-, second- and third-line medications, this refers to the group, rather than individual patient, level. In other terms, meta-analytic evidence from NMAs, and recommendations in some guidelines (e.g., NICE) suggest that methylphenidate should be the first line option, but for specific patients, medications other than methylphenidate would be the preferred ones. Unfortunately, currently no reliable predictors (socio-demographic, behavioral, neuropsychological, genetic, neuroimaging, or neurophysiological) of response have been identified. Second, while there is evidence that optimization of the dose is key, the maximum safe and effective doses, possibly beyond those currently recommended, are not well understood. Third, evidence from RCTs on augmenting strategies is still limited. Fourth, while several alternative formulations (e.g., transdermal, oral) of methylphenidate or stimulants are currently being developed and approved, no novel agents with the same of higher effect size of stimulants, in terms of efficacy, but with better tolerability profile and lower abuse potential, have been found.

13.2. Research potential: the ultimate goal in this field?

Based on the points presented in the previous sections, it is fair to state that currently the pharmacological management of ADHD still relies, at least in part, on a trial-and-error process in the use of a limited number of available medications that are not curative. Ideally to field should aim to (1) implement precision psychiatry approaches based on reliable prediction models [42] in order for clinicians to better use currently available medications, and, if needed, their combination, based on the specific characteristics of the patient; (2) develop additional agents that are better linked to the etiopathophysiology of the disorder and can address more globally the functioning of the individual, rather than the core symptoms exclusively in a symptomatic way.

13.3. What is needed to achieve this goal and what is the biggest challenge?

In relation to the first goal defined in the previous section, similarly to what is being implemented in other field, e.g., antidepressants, analyses based on large dataset including individual patient data from RCTs coupled with data from observational studies should be considered [43]. Importantly, preferences of patients will need to play a crucial role in designing algorithms that can provide indications on the most appropriate medications at patient individual level [44]. These large datasets will then need to be analyzed with advanced statistical approaches including machine learning or machine learning coupled to more traditional statistical approaches. While these approaches are being developed and validated [45], perhaps the biggest challenge will be to promote and implement a cultural shift in the field, to stimulate open science and data sharing practices that will make such large datasets possible.

In terms of developing and testing new medications, it will be crucial to stratify patients based on clinical and neurobiological characteristics to develop compounds addressing etiopathophysiological targets altered in specific subgroups of individuals with ADHD. This will move forward the pharmacotherapy of ADHD from a 'one size fits all' to a 'precision psychiatry' approach. It would be interesting also to assess the effects of ADHD pharmacological treatments combined with neurostimulation (e.g., repetitive transcranial magnetic stimulation, rTMS, or direct transcranial direct current stimulation, that may bring more long-lasting changes in the brain, even though currently there is no evidence to support the use of these methods in ADHD [41]).

13.4. What is going to happen in the next few years

To achieve the aims discussed in the previous section, it is hoped that there will be collaborative efforts from consortia, rather than just research studies conducted by single groups or single manufacturers. Moreover, precision psychiatry models will hopefully be tested in randomized controlled trials that will establish their cost-effectiveness before they can enter the real of the daily clinical practice. Alongside further testing of alternative formulations of stimulants and of medications that are currently being tested in phase 2–3 RCTs [42], it is possible that novel compounds will be tested in selected, more homogeneous (based on clinical or neurobiological characteristics) groups of patients, to find effective agents, well tolerated and with no potential of abuse. Furthermore, it is likely that the number of RCTs in pre-schoolers with ADHD will increase [46], as there is increasing attention to this age group to hopefully implement early and effective prevention/treatment strategies.

13.5. Any particularly interesting areas of research?

Among the many areas of research, two are highlighted here

(1) Even when precision psychiatry approaches will be implemented, it will be necessary to continuously and routinely measure their impact in daily clinical practice. In this regard, outcome-based care studies will be crucial. Based on meta-analytic evidence, some in the field (e.g. [47]) have proposed neuropsychological functions as additional outcome other that measurement of the severity of the behavioral symptoms, to (1) gain insight into the effects of treatments on neuropsychological functions; (2) identify additional indicators of early, subclinical changes; and (3) provide objective and hence less biased measures of effects of the treatments.

(2) In terms of evidence related to the development of new medications, interestingly, it has been found [48] that none of the genes encoding molecules that are the target of currently licensed medications for ADHD are significantly associated with this disorder, suggesting that licensed medications probably act through different mechanisms than those underlying ADHD. It has been proposed [48] to identify genes/genetic pathways ('druggable genes') involved in the biological processes underpinning ADHD that can be targeted by medications. In a seminal work, three loci on chromosomes 1, 4, and 12 were found to have significant association with ADHD and contained nine druggable genes. Pursuing this line of research will hopefully lead to agents with more tangible effects on the symptoms, beyond symptomatic relief.

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Declaration of Interest

Reviewer Disclosures

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